REMARKS

I. Status of the Claims

Claims 1-88 are pending in the application, and claims 1-29, 57-66, 68-82 and 84-88 have been examined. Claims 1, 2, 4-29, 57-66, 68-82 and 84-88 stand rejected under 35 U.S.C. §112, first paragraph. Claims 21, 28, 57-66, 68 and 87 stand rejected under 35 U.S.C. §112, second paragraph. Claims 1-3, 14, 15, 22, 23, 27, 57-58 and 87 are rejected under 35 U.S.C. §102 over Shriver *et al.*

II. Rejection Under 35 U.S.C. §112, First Paragraph

The examiner that claims 1, 2, 4-29, 57-66, 68-82 and 84-88 lack enablement. More specifically, the rejection stems from the examiner's belief that the specification only supports detection of loss of heterozygosity in RPL14 in non-small cell lung carcinoma. Applicants traverse.

The claims have all been amended to recite RPL14 probes and examination of loss of heterozygosity. However, the claims have not been limited to NSCLC, but instead to lung cancers generally. As noted by the examiner, Shriver *et al.* "teaches chromosome 3p is consistently deleted in lung cancer ...." Moreover, the examiner has seen fit to reject claim 3 over Shriver *et al.*, arguing again that the examiner believes lung cancers in general to be addressed by the reference.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 21, 28, 57-66, 68 and 87 stand rejected under the second paragraph of §112 as indefinite.

Claims 21 and 28 are said to be indefinite in reciting "the probe of Claim 1." An amendment to each claim is offered to replace the language objected to.

Claims 57-66 are rejected as allegedly lacking a process step that satisfies the preamble. An amendment is offered to claim 57 that is believed to clarify the claim.

Claim 68 uses the term "lung of cancer," which is allegedly indefinite, and for alleged failure to recite a step that relates to the premable. The claim has been canceled.

Claim 87 stands rejected as allegedly "not clearly indicat[ing] how an individual is identified to be segregated from a high risk environment." The claim has been amended to clarify the subject matter.

Reconsideration and withdrawal of the rejections is respectfully requested.

IV. Rejection Under 35 U.S.C. §103

Claims 1-3, 14, 15, 22, 23, 27, 57-58 and 87 are rejected under 35 U.S.C. §102 over Shriver *et al.* Specifically, the examiner argues that Shriver teaches that the 3p region is consistently deleted in cancers, and that the RPL14 gene, which lies in this region, is deleted in a high percentage of lung cancers. Finally, Shriver is said to state that "RPL14 is an important event in lung carcinogenesis ...." Applicants traverse.

Applicants first point out that none of the rejected claims are drawn to a method of detecting cancer. Rather, claim 1 is drawn to identifying a subject at risk of lung cancer, claim 57 is drawn to a method for predicting progression or metastasis of lung cancer, claim 69 is drawn to predicting lung cancer relapse or development of new primary lung cancer, and claim

87 is drawn to a method of identifying an individual to be segregated from a high risk lung cancer environment. Thus, the mere fact that Shriver examined cancerous cell lines and found that the contained deletions in RPL14 does not suggest that one would find these same lesions in non- or pre-cancerous cells.

Moreover, applicants take exception to the examiner's characterization of Shriver as ***teaching*** the importance of RPL14 in lung carcinogenesis. Here is the precise statement that Shriver made on this topic: "Additional analysis is needed to determine if functional loss of ribosomal protein RPL14 is an important event is lung and oral carcinogenesis ...." Thus, Shriver admits that the data provided do ***not*** demonstrate this link – a link that is reflected in each of the pending claims.

In contrast, the instant application shows data nowhere found in Shriver – data demonstrating a link between cancer risk and RPL14:

> *Results.* These results showed that in patients without evidence of lung cancer/squamous atypia, who had a history of smoking, a deletion of 3p21.3 existed that roughly paralleled the number of pack years smoked indicating that this deletion may occur secondarily to exposure to tobacco smoke, and also may be an early event in neoplastic transformation. None of these patients have yet to evidence clinical or straight chest X-ray evidence of lung cancer, however, those with the highest levels of deletion may be at high risk to develop neoplasia.
>
> In patients with atypia as manifested by squamous metaplasia or atypia, the level of deletion was higher than in the negative group, with the highest levels of deletion noted in patients with carcinoma.

> The results also correspond with previous studies with 3p21.3 probe for chromosomal aberrations in microdissected lung carcinomas and adjacent "normal" bronchial cells. Genetic instability is a very early event in tumorigenesis and chromosomal numerical abnormalities are associated with smoking. 3p21.3 deletions occurred more frequently in the lung tumors and adjacent bronchi of the patients who smoked than in control lung tissue from patients who did not smoke. Smoking may cause molecular damage much earlier than the corresponding manifestation of neoplasia at a morphologic level. Smoking is a major etiologic factor for the development of lung cancer and based on the studies presented herein, the loss of 3p21.3 is an early event in the tumorigenesis of lung cancer.

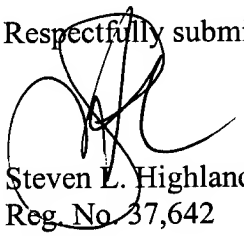
Specification, Example 6. This sort of analysis is wholly lacking from the Shriver reference, and bears directly upon the patentability of the present claims. Thus, applicants respectfully submit that Shriver ***does not*** teach the relevance of RPL14 (or 3p21.3) in identifying individuals ***at risk*** of developing cancer. Reconsideration and withdrawal of the rejection is respectfully requested.

Applicants note that claims 29, 66 and 88 were not included in this rejection. Given the amendments (to address §112 issues) to independent claims 1, 57 and 87, from which clams 29, 66 and 88 depend, respectively, it is believed that these claims are in condition for allowance. Moreover, claims 3, 58 and 81 now present similar subject matter (combination analysis with a second gene probe), albeit direct to the GC20 gene. In addition, claim 69, and claims dependent thereon, were also not rejected over Shriver *et al.* This claim also has been amended to address §112 issues. As such, it is believed that these claims are allowable for additional reasons beyond those set forth above.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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APPENDIX A: MARKED UP COPY OF AMENDED CLAIMS

1. (Amended) A method for identifying a subject at risk for the development of lung cancer comprising:

(a) obtaining a test sample from a subject;
(b) providing an RPL14[, CD39L3, PMGM, or GC20] gene probe;
(c) contacting said probe with said test sample; and
(d) analyzing DNA from said test sample for loss of heterozygosity in RPL14,

whereby [aberrations in the hybridization of said probe to said DNA] loss of RPL14 heterozyosity, [as compared to wild-type DNA,] indicates risk for the development of lung cancer.

2. (Amended) The method of claim 1, wherein said test sample comprises a surgical or biopsy specimen, a paraffin embedded tissue, a frozen tissue imprint, a sputum, [a lavages, a peripheral blood lymphocytes, a urinary specimen such as a bladder washing and urine,] esophageal brush, a fine needle aspiration, a buccal smear or a bronchial lavage.

3. (Amended) The method of claim 1, [wherein said cancer is lung cancer] further comprising providing a GC20 gene probe and performing steps (c) and (d) with said GC20 gene probe.

4. (Canceled)
5. (Canceled)
6. (Canceled)
7. (Canceled)
8. (Canceled)
9. (Canceled)
10. (Canceled)

19. (Amended) The method of claim 1, further comprising administering to said subject chemopreventive drugs, nutritional supplements, chemotherapeutic drugs or biological modifying [respdase] response drugs.

21. (Amended) The [probe] method of claim 1, wherein said probe is used to identify subjects who are suitable for novel investigational therapeutic approaches.

28. (Amended) The [probe] method of claim 1, wherein said probe is used as a biomarker for the early detection of early neoplastic events or cancer.

29. (Amended) The method of claim 1, further comprising providing a 10q22 DNA gene probe and performing steps (c) and (d) with said 10q22 gene probe.

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. (Canceled)

37. (Canceled)

38. (Canceled)

39. (Canceled)

40. (Canceled)

41. (Canceled)

42. (Canceled)

43. (Canceled)

44. (Canceled)

45. (Canceled)

46. (Canceled)

47. (Canceled)

48. (Canceled)

49. (Canceled)

50. (Canceled)

51. (Canceled)

52. (Canceled)

53. (Canceled)

54. (Canceled)

55. (Canceled)

56. (Canceled)

57. (Amended) A method for predicting the progression or metastasis of non-small cell lung carcinoma and other carcinoma in a subject having said non-small cell lung carcinoma comprising:

(a) obtaining a test sample from a subject;

(b) providing an [RPL14, CD39L3, PMGM, or GC20] gene probe;

(c) contacting said probe with said test sample; and

(d) analyzing DNA from said test sample for loss of heterozygosity in RPL14,

wherein loss of RPL14 heterozygosity predicts progression or metastasis of said non-small cell lung carcinoma.

58. (Amended) The method of claim 57, [wherein said cancer is lung cancer] further comprising providing a GC20 gene probe and performing steps (c) and (d) with said GC20 gene probe.

59. (Canceled)

60. (Canceled)

61. (Canceled)

62. (Canceled)

63. (Canceled)

64. (Canceled)

65. (Canceled)

66. (Amended) The method of claim 57, further comprising [using] providing a 10q22 DNA probe and performing steps (c) and (d) with said 10q22 gene probe.

67. (Canceled)

68. (Canceled)

69. (Amended) A method of [determining likelihood of] predicting lung cancer relapse or development of a new primary lung cancer in a subject comprising determining [genetic aberrations at chromosomal loci 3p21.3 or 10q22 in DNA] loss of heterozygosity in the RPL14 gene in cells of bronchial tissue adjacent to tumor tissue from said subject, wherein [abnormalities in DNA of] loss of RPL14 heterozygosity in said adjacent tissue [correlate with] predicts lung cancer relapse or development of [said] lung cancer.

71. (Amended) The method of claim 70, wherein said cancer is non-small cell lung carcinoma.

72. (Canceled)

73. (Canceled)

74. (Canceled)

75. (Canceled)

76. (Canceled)

77. (Canceled)

78. (Canceled)

79. (Canceled)

80 (Canceled)

81. (Amended) The method of claim 69, [wherein an RPL 14, CD39L3, PMGM, or] further comprising providing a GC20 gene probe and determining loss of heterozygosity in the GC20 gene in cells of bronchial tissue adjacent to tumor tissue from said subject.

82. (Canceled)

83. (Canceled)

84. (Amended) The method of claim [82] 69, further comprising [use of] providing a 10q22 DNA probe and determining loss of heterozygosity in the 10q22 region in cells of bronchial tissue adjacent to tumor tissue from said subject.

87. (Amended) A method of identifying an individual to be segregated from a high risk lung cancer environment comprising:

(a) obtaining a test sample from a subject;
(b) providing an RPL14[, CD39L3, PMGM, or GC20] gene probe
(c) contacting said probe with said test sample; and
(d) analyzing DNA from said test sample for loss of heterozygosity in RPL14,

whereby [said analysis is used to identify] loss of RPL14 heteroygosity identifies an individual who is highly susceptible to the development of lung cancer and who should not be exposed to a high risk environment.

88. (Amended) The method of claim 87, further comprising providing a 10q22, GC20 or PTEN/MMAC1 gene probe and performing steps (c) and (d) with said 10q22, GC20 or PTEN/MMAC1 gene probe.